IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Carl-Axel Bauer *et al.* Art Unit : 1617
Serial No. : 10/010,283 Examiner : Jennifer Kim
Filed : November 13, 2001
Title : NEW USE FOR BUDESONIDE AND FORMOTEROL

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JAN TROFAST, PH.D.

I, Jan Trofast, declare as follows:

1. I have been a scientist at AstraZeneca R&D (formerly Astra AB) since 1979 in the division of Medicinal Chemistry and Pharmaceutical & Analytical R&D. I received a Ph.D. in organic chemistry in 1978 from Lund Institute of Technology, Lund, Sweden. I have been studying and conducting research in the field of respiratory disorders since 1979, and I am an expert in this field. I am a co-inventor of the invention claimed in this application.

2. In collaboration with AstraZeneca, a placebo-controlled 12 month clinical trial was performed using a combination of budesonide/formoterol fumarate dihydrate (under the product name Symbicort®) in the treatment of moderate to severe COPD. Formoterol is the biologically active moiety in formoterol fumarate dihydrate (FFD). This study is published in Calverley *et al., Eur. Respir. J.* 22:912-919, 2003. In summary, before randomization, 1022 patients were treated in a 2 week initial run-in period with oral prednisolone (30 mg once daily), inhaled FFD (Oxis®; 2 puffs twice per day, each puff delivering 4.5 μg FFD to the patient from a metered dose[1] of 6.0 μg FFD), and terbutaline as needed (Bricanyl®; 0.5 mg by inhalation). The patients had the following profile:

[1] A "metered dose" is the amount of product that is positioned in the inhaler for delivery to the patient with each puff. Not all of the metered dose is delivered to the patient; some product will stick to the sides of the inhaler, or

Age $\geq$ 40 years

COPD diagnosis since at least 2 years prior to the study

At least 10 pack years smoking history[2]

Documented use of inhaled bronchodilators as a quick relief medicine

At least one severe COPD exacerbation within 2-12 months of entry

$FEV_1 \leq 50\%$ predicted normal, pre-bronchodilator

$FEV_1/VC \leq 70\%$ pre-bronchodilator

(FEV_1 = Forced Expiratory Volume within 1 second, VC = vital capacity)

All of the following medications and the placebo were delivered from a Turbuhaler® inhaler. The patients were randomized into four groups and treated as follows:

Group 1: Budesonide/FFD combination (Symbicort®; 2 puffs twice per day, each puff delivering 160 µg budesonide/4.5 µg FFD to the patient (corresponding to a metered dose of 200 µg budesonide and 6.0 µg FFD respectively for the monoproducts))

Group 2: Budesonide alone (Pulmicort®; 2 puffs twice per day, each puff delivering 160 µg budesonide to the patient from a metered dose of 200 µg budesonide)

Group 3: FFD alone (Oxis®; 2 puffs twice per day, each puff delivering 4.5 µg FFD to the patient from a metered dose of 6.0 µg FFD)

Group 4: Inhaled placebo composition (2 puffs, twice daily, no active ingredients)

The patients were studied for 12 months, with various measures of COPD symptoms being regularly recorded.

3. The results of this study suggest that the combination of budesonide and FFD produces several synergistic effects.

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will otherwise remain in the inhaler. A "delivered dose" is the amount of product that exits the inhaler. This amount is less than the metered dose.

[2] As understood in the art, "10 pack years" indicates that the individual smoked a pack a day for 10 years, or 2 packs a day for 5 years, etc.

For example, as shown in the graph titled "Symbicort reduces the risk of first exacerbation requiring medical intervention"[3] (Appendix 1, submitted herewith), the hazard rate was reduced (compared to placebo) by **28.5 %** in patients treated with the budesonide/FFD combination. The corresponding reduction for patients treated with budesonide alone was **7.5 %**, while FFD alone actually produced an increase (compared to placebo) of **1.5 %**. A merely additive effect would have produced a 6.0 % reduction[4]. These data are presented in Calverley *et al.* at page 915, column 1 and in Figure 1. The data in Table 3 of Calverley *et al.* supplement these results.

4. The enclosed graph titled "Symbicort reduces the number of severe exacerbations/patient/year" (Appendix 2, submitted herewith) also strongly imply a synergistic effect of the budesonide/FFD combination therapy. As compared to treatment with placebo, treatment with FFD alone actually increased the number of exacerbations per patient per year slightly (**+3%**), while treatment with budesonide alone decreased the number of exacerbations per patient per year by **12%**. **Patients treated with the budesonide/FFD combination, however, exhibited a 24% reduction in exacerbations.** This result demonstrates a synergistic effect, as the 24% reduction is much greater than the 9% reduction expected if the effect of the combination therapy were merely additive. These data were presented previously in the declaration of Christer Hultquist, filed December 13, 2002, and supplement the data presented in Calverley *et al.* at page 915, column 1.

5. A synergistic effect was also indicated in the patients' need for oral steroids during the course of the study, as shown in the graph titled "Symbicort reduces need for oral steroids"

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[3] Severe exacerbations were considered to be exacerbations requiring medical intervention, *i.e.* administration of antibiotics and/or oral steroids, and/or hospitalization due to respiratory symptoms.

[4] In order to assure the stability of the first order approximation used above to assess the additive effects, a fully elaborated approach is also presented. By treating these data in a multiplicative way (the model being relative), the additive effect of budesonide and formoterol is = 100 – (100-7.5)*(100+1.5)/100 = 6.1 % and the combination (Symbicort) over this is = 100 - 100*100*(100-28.5)/((100-7.5)*(100+1.5)) = 23.8 %. Note that this effect is even greater than suggested above (= 28.5-6.0 = 22.5 %), showing that calculation on the additive scale gives a conservative estimate. The same kind of multiplicatory calculations will give essentially the same result on items 4, 5, 9 and 11 below; other items below should use the additive model.

(Appendix 3, submitted herewith). Treatment with budesonide alone reduced the hazard rate of time to first oral steroid use by **14%** compared to placebo, and treatment with FFD alone reduced the hazard rate by **13%** as compared to placebo. **In contrast, treatment with the budesonide/FFD combination reduced the hazard rate of time to first oral steroid by 42.3% versus placebo.** This is far better than the 27% reduction that would have been expected from an additive effect of the individual budesonide and FFD components. These data supplement the data presented in Calverley *et al.* at page 915, column 1 (recalculated to placebo).

6. A synergistic effect was also indicated in the effect on night awakenings, as shown in the graph titled "Symbicort increases nights without awakenings" (Appendix 4, submitted herewith). Treatment with either budesonide alone or FFD alone resulted in an adjusted mean change in awakenings-free nights of **+3.7 %** (compared to placebo). If budesonide and FFD in combination had a merely additive effect on the change in awakenings-free nights, the adjusted mean change of the combination therapy (compared to placebo) would be expected to be **+7.4 %.** However, treatment with the combination therapy resulted in an adjusted mean change in awakenings-free nights (compared to placebo) of **+ 9.2 %,** much greater than the calculated additive effect of 7.4 %.

7. A synergistic effect was also indicated in the morning peak expiratory flow (PEF), as shown in the graph titled "Symbicort rapidly improves and maintains morning PEF" (Appendix 5, submitted herewith). The difference in adjusted mean change of morning PEF, as compared to placebo, was **3.5** L/min for the patients treated with budesonide alone, **11.1** L/min for those treated with FFD alone, **and 18.3 L/min for the patients treated with the budesonide/FFD combination,** *i.e.*, 3.7 L/min higher than would be expected if the effect were merely additive. These data were presented previously in the declaration of Christer Hultquist, filed December 13, 2002, and supplement the data presented in Calverley *et al.* at page 916, Figure 3(a).

8. The graph titled "Symbicort rapidly improves and maintains evening PEF" (Appendix 6, submitted herewith) strongly imply a synergistic effect on the patients' evening

peak expiratory volume (PEF). The difference in adjusted mean change of evening PEF, as compared to the placebo, was **2.0** L/min for the patients treated with budesonide alone, **8.9** L/min for those treated with FFD alone, and **14.1 L/min for the patients treated with the budesonide/FFD combination**, *i.e.*, 3.2 L/min higher than would be expected if the effect of the budesonide/FFD combination were merely additive. These data are graphically represented in Calverley *et al.* at page 916, Figure 3(b), and recalculated to placebo for easier comparison.

9. The graph titled "Symbicort produces rapid and maintained improvement in lung function (FEV1)" (Appendix 7, submitted herewith) illustrates that FEV1 decline was less severe in patients treated with a budesonide/FFD combination therapy than in those treated with either monotherapy. The combination therapy was **14%** better than placebo in this regard, while the monotherapies were respectively only **8%** and **2%** better than placebo. These data are presented in Calverley *et al.* at page 915, column 2 and in Figure 2.

10. As illustrated by the graph titled "Symbicort improves health related quality of life, HRQL" (Appendix 8, submitted herewith), the mean change in total score on St. George's Respiratory Questionnaire (SGRQ) as compared to placebo was **-7.5**, which was a greater improvement than that observed following treatment with budesonide alone (**-3.0**) or FFD alone (**-4.1**)[5]. These data are reported in Calverley *et al.* at page 916, column 2 and in Figure 4.

11. As illustrated by the graph titled "Symbicort reduces discontinuations compared to other treatments" (Appendix 9, submitted herewith), fewer patients withdrew from the study when they received the budesonide/FFD combination therapy than with either of the monotherapies. These data supplement the data in Table 1 of Calverley *et al.* at page 914, which reports that **71%** of the patients originally enrolled in the study and who received treatment with the combination of budesonide and FFD completed the study. By comparison, only **59%** of patients receiving placebo completed the study, approximately the same as those receiving FFD alone (**56%**) or budesonide alone (**60%**). The multiple beneficial effects described above may

[5] A change of *minus* 4 points in the SGRQ represents a clinically important improvement in health related quality of life. The more negative the score, the better the quality of life.

have contributed to the fact that fewer patients receiving the budesonide/FFD combination therapy withdrew from the study. The numbers could be obtained in the graph by looking at the fraction of subjects in study at the end of the twelve month period (see also the bottom line of Table 1 at page 914 of Calverley *et al.*).

12. Taken together, the overall consistency in these variables, describing different but clinically important aspects of the disease, strongly suggests that the combination produces synergistic effects.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

By: Jan Trofast
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Date: 2 Nov. 2005

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